Preoperative moderate to severe diastolic dysfunction: A novel Doppler echocardiographic long-term prognostic factor in patients with severe aortic stenosis

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Objective: We studied long-term outcomes in severe aortic stenosis and the importance of prosthesis type (mechanical vs biologic) and size, preoperative left ventricular ejection fraction, diastolic function, and left ventricular mass.

Methods: Patients undergoing valve replacement from 1991 to 1993 (n = 399, 45% women) were included. The diastolic function was evaluated by integrating mitral and pulmonary venous flow data with Doppler echocardiography. The patients were classified as having either normal diastolic function to mild diastolic dysfunction or moderate to severe diastolic dysfunction. Left ventricular ejection fraction and the diastolic function category were incorporated together with age, sex, and time since operation into a Poisson regression model with death as the end point. Prosthesis type and size and left ventricular mass were also investigated.

Results: The age (mean ± SD) was 71 ± 9 years, and the overall survival after 12 years was 50%. Although markedly reduced during the initial 6-month period, mortality risk subsequently increased more than could be explained by age (hazard ratio of 1-year difference = 1.12, $P = .0005$). The moderate to severe diastolic dysfunction pattern independently predicted late mortality (hazard ratio = 1.72, $P = .0038$), whereas left ventricular ejection fraction did not (hazard ratio = 0.99, $P = .18$). The prognostic importance of moderate to severe diastolic dysfunction did not diminish with time; on the contrary, it tended to increase. Mortality after 12 years was not predicted by left ventricular mass ($P = .66$), prosthesis type ($P = .57$), or prosthesis size ($P = .58$).

Conclusion: This study reveals that moderate to severe diastolic dysfunction in patients with aortic stenosis is an independent predictor of late mortality after valve replacement and that its importance does not decrease with time. Our findings may suggest that moderate to severe diastolic dysfunction implies nonreversible myocardial changes that negatively affect survival.

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Supported by grants from the Göteborg Medical Society, Sahlgrenska University Hospital, the Västra Götaland Region, the Swedish Heart and Lung Foundation, and the Swedish Medical Society.

Received for publication June 3, 2004; revisions accepted Aug 28, 2004; accepted for publication Sept 3, 2004.

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J Thorac Cardiovasc Surg 2005;129:890-6

0022-5223/$30.00

doi:10.1016/j.jtcvs.2004.09.004

According to guidelines, patients with severe aortic stenosis should undergo aortic valve replacement if they have symptoms,[1] but the treatment of symptom-free patients is more controversial.[2,3] It can be difficult in clinical practice to distinguish between patients with and without symptoms, because the progression of stenosis is slow, the patients adapt, and, especially in the case of older patients, symptoms such as dyspnea are often not recognized and communicated. Other prognostic factors may therefore play an important part in the decision-making process.

In patients with aortic stenosis, several clinical risk factors have been identified; these include myocardial infarction, coronary artery disease, atrial fibrillation, congestive heart failure, and aortic regurgitation.[4-6] Patients with aortic stenosis are known to have left ventricular hypertrophy and diastolic dysfunction. The type and size of aortic prosthesis determine the degree of regression of left ventricular mass (LVM) after aortic valve replacement.[7-9] The reduction in LVM has been shown to be more pronounced with mechanical prostheses than with biologic prostheses and also to be more pronounced with large prosthetic valves than with small (≤21 mm) ones.[9] It is therefore an unproven hypothesis that the combination of excessive left ventricular hypertrophy and a small mechanical valve or stented biologic prosthesis could adversely influence long-term outcome.

In a previous report on prognostic factors of importance for early mortality, we found that moderate to severe diastolic dysfunction did not increase early mortality.[10] However, to our knowledge, the prognostic value of moderate to severe diastolic dysfunction in terms of long-term outcome evaluated with Doppler echocardiography has not been studied. We therefore investigated the long-term outcome of severe aortic stenosis and the importance of preoperative left ventricular function, LVM, and prosthesis type (mechanical or biologic) and size in consecutive patients. Because the prognostic importance of these parameters can be expected to change with time, we applied a special statistical method (Poisson regression) that enabled us to evaluate temporal changes in risk prediction.

Methods

Subjects

Between January 1991 and December 1993, a total of 648 patients from western Sweden were admitted to Sahlgrenska University Hospital for aortic valve replacement. We excluded 195 patients with a maximum gradient less than 60 mm Hg and a calculated effective orifice area greater than 1.0 cm^2, more than moderate (>grade 2/4) aortic or mitral regurgitation, or signs of mitral stenosis. Fifty-four patients with incomplete preoperative data were excluded. The echocardiographic investigations of the remaining 399 patients were reevaluated by two experienced examiners. The mortality during the 12-year follow-up period was investigated, and death certificates were collected through the Swedish National Board of Health and Welfare. The study was approved by the human ethics committee at Sahlgrenska University Hospital.

M-mode and 2-Dimensional Echocardiography

Preoperative echocardiography was performed with an Acuson 128 or 128XP Computed Sonograph (Acuson Corporation, Mountain View, Calif). M-mode measurements were made according to the recommendations of the American Society of Echocardiography. LVM was calculated with the cube formula,[11] and the left ventricular ejection fraction (LVEF, [diastolic volume−systolic volume]/diastolic volume × 100%) was calculated either according to the Simpson rule or according to Teichholtz. In patients in whom the LVEF could not be calculated, a visual estimation of the LVEF was made (performed in 7% of cases). Planimetry of the left atrium was performed on line from a late systolic stop frame. The left ventricular outflow tract diameter was measured from a parasternal long-axis view.

Doppler Measurements

Blood flow velocity in the left ventricular outflow tract was estimated by pulsed-wave Doppler from an apical four-chamber view. Mitral flow was recorded between the mitral leaflets in the four-chamber view. From the mitral velocity tracings, early flow velocity *(E),* the deceleration time of E wave, and peak velocity during atrial systole *(A)* were measured. The E/A ratio was calculated. Pulmonary venous flow velocities were obtained from the upper right pulmonary vein. Peak velocities during systole *(S)* and diastole *(D)* were measured. The S/D ratio was calculated. Continuous wave Doppler signals were recorded from multiple windows. The stroke volume was calculated as the product of the cross-sectional area of the left ventricular outflow tract and the velocity time integral. Pressure gradients were calculated according to the simplified Bernoulli equation, and the effective orifice area was calculated according to the continuity principle.

Patterns Describing Diastolic Function

The diastolic function was evaluated by integrating mitral flow and pulmonary venous information.[12] Four different filling patterns were described: type A, normal diastolic function (normal mitral E/A and S/D ratios); type B, mild diastolic dysfunction (reduced E/A ratio and normal S/D ratio); type C, moderate diastolic dysfunction (normal E/A ratio [pseudonormalization] and reduced S/D ratio); and type D, severe diastolic dysfunction (increased E/A ratio and reduced S/D ratio). The patients were then divided into two groups: those with normal diastolic function to mild diastolic dysfunction (types A and B), who are likely to have normal filling pressure, and those with moderate to severe diastolic dysfunction (types C and D), who often have increased left ventricular filling pressure.[12] The graded assessment of diastolic function requires sinus rhythm, and patients with atrial fibrillation were therefore excluded. The mitral and pulmonary venous flow patterns are age dependent. A healthy control group (n = 71, age 18-83 years, 59% men) without hypertension or diabetes mellitus, with a normal resting electrocardiogram, and without a history of heart disease was compared with the study group.

Statistical Analyses

Continuous variables are expressed as mean ± SD. Categoric variables are summarized with the use of proportions. The mean of 3 M-mode and Doppler measurements was used in patients with sinus rhythm and the mean of 5 measurements was used in patients with atrial fibrillation. An unpaired Student *t* test was used to compare continuous data, whereas the χ^2 test was used to compare categoric data.

The death hazard function was estimated with a Poisson model depending on a set of variables.[13] With this model, it is possible to evaluate the prognostic importance of a variable and evaluate whether it changes with time. The hazard function was of the form $\exp(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k)$, where $\beta_1, \beta_2, \ldots, \beta_k$ were

TABLE 1. Mortality risk estimated by a Poisson model including age, sex, different time intervals, and diastolic function

	β	SE	*P* value
Constant	−6.99	1.00	<.0001
Current age	0.09	0.01	<.0001
Sex	−0.21	0.17	.23
Min(time, 1/12)*	−23.6	7.09	.0009
Max[min(time-1/12, 0.5-1/12), 0]†	−3.48	1.41	.01
Max(time-0.5, 0)‡	0.12	0.03	.0005
Moderate to severe diastolic dysfunction	0.54	0.18	.0023

*Reflecting change in risk per year during first month after surgery.
†Reflecting change in risk per year during second through sixth months after surgery.
‡Reflecting change in risk per year at more than 6 months after surgery.

coefficients and $x_1, x_2, \ldots, x_k$ were the values of the variables. The quantity $\exp(\beta)$ gives the hazard ratio (HR) of a difference of 1 unit of the corresponding variable. The analysis was performed in stepwise fashion. The following variables were included: age, sex, time since surgical treatment, LVEF, normal diastolic function to mild diastolic dysfunction (value of 0) versus moderate to severe diastolic dysfunction (value of 1), prosthesis type, prosthesis size, and LVM. In the last step, only the variables of significant importance ($P < .05$) were included.

Diastolic function parameters are known to be age dependent. From the healthy control subjects, a regression equation including age was calculated, as well as the residuals. For each patient in the study group, the expected E/A ratio and S/D ratio were predicted. The observed E/A ratios and S/D ratios in patients were regarded as being reduced or increased if they differed by more than 1.96 SD from the predicted value by *Z* score.

Results

Clinical and Echocardiographic Characteristics

The age at the time of operation was 71 ± 9 years, and 45% of the patients were women. Only 2.5% of the patients were younger than 50 years (10/399), whereas 12.5% were younger than 60 years (50/399). Forty percent underwent combined aortic valve replacement and coronary artery bypass grafting procedures, and 16% had atrial fibrillation. Thirty percent (n = 118) received a stented biologic prosthesis (Biocor; St Jude Medical Inc, Minneapolis, Minn) and, among those who received a mechanical prosthesis (n = 279), 228 patients received a St Jude Medical Standard prosthetic valve (St Jude Medical Inc), 45 an OmniCarbon (Medical Incorporated, Inver Grove Heights, Minn), and 5 a Carbomedics (Sulzer Carbomedics Inc, Austin, Tex). The mean size of the biologic prosthesis was 24 ± 1.6 mm; that of the mechanical prosthesis was 22.8 ± 2.2 mm. Thirty-one percent received a small prosthesis (≤21 mm), and only 8 patients received a stented biologic valve of size 21. Twenty-four percent of the patients had a reduced LVEF (<50%), 30% had moderate to severe diastolic dysfunction, and another 12% had mild diastolic dysfunction.

The median follow-up was 9.4 years (range 0-12 years). The overall survival after 12 years was 50%. The early (<30 days) mortality was 4% (n = 17). Autopsy was performed on 15 patients who died during follow-up (8%).

Mortality Risk

The mortality risk was markedly reduced during the initial 6-month period, but it then increased more than could be explained by age (Table 1). The yearly increase in mortality risk was 12% (HR of 1-year difference 1.12, $P = .0005$). Moderate to severe diastolic dysfunction was identified as an independent predictor (HR 1.72, $P = .0038$). Patients with moderate to severe diastolic dysfunction had a 72% increase in mortality risk relative to those with normal diastolic function or mild dysfunction. LVEF did not independently predict mortality (HR 0.99, $P = .18$) but contributed significantly (HR 0.986, $P = .0038$) when moderate to severe diastolic dysfunction was omitted from the regression model. Figure 1 shows the importance of increased moderate to severe diastolic dysfunction and age.

The effect of preoperative moderate to severe diastolic dysfunction on the mortality risk did not decrease with time (Table 2). On the contrary, there was a tendency for the importance of preoperative dysfunction to increase with time. Figures 2 and 3 are based on the results of the Poisson model presented in Table 2. For a 65-year-old woman with preoperative moderate to severe diastolic dysfunction, there was a tendency for the annual incidence of death to increase (Figure 2). For patients with normal diastolic function to mild dysfunction, the probability of survival did not differ from that of the general population after the first six-month period (Figure 3). For patients with moderate to severe diastolic dysfunction, however, the probability of survival continued to deviate from that of the general population. The estimated risk ratio for death between moderate to severe diastolic dysfunction and normal diastolic function to mild dysfunction was 1.60 after 2 years; it increased to 1.90 after 10 years.

LVM did not predict mortality ($P = .42$), nor did prosthesis type ($P = .42$) or size ($P = .58$). We hypothesized that the combination of left ventricular hypertrophy and small prosthesis size or biologic prosthesis could adversely influence mortality, but these high *P* values excluded any interaction, and further analyses were not performed.

Left Ventricular Diastolic Function

Patients with moderate to severe diastolic dysfunction were older, with a lower LVEF and cardiac output (Table 3) compared with others. Patients with moderate to severe diastolic dysfunction had a larger left atrium and a higher systolic tricuspid valve gradient, indicating higher pulmonary arterial pressure. The percentages of biologic prosthe-

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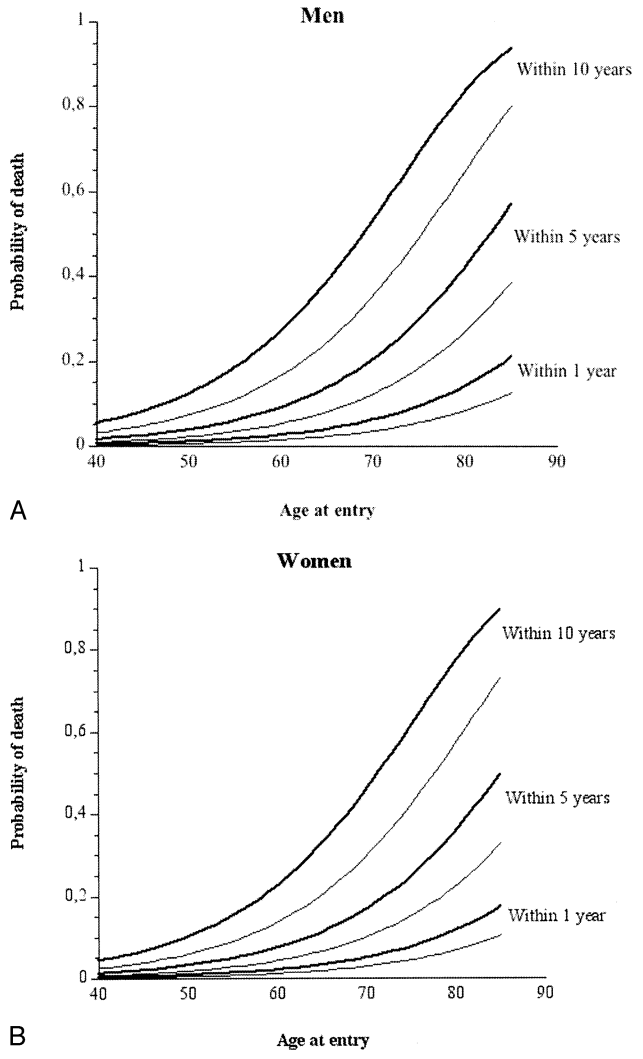

Figure 1. Importance of moderate to severe diastolic dysfunction *(bold lines)* compared with normal diastolic function to mild dysfunction *(narrow lines)* and age at entry for probability of death within 1 year, 5 years, and 10 years. A, Results for men. For a 70-year-old male patient, probability of death within 10 years increases from approximately 35% with normal diastolic function to mild dysfunction to 53% in those with moderate to severe diastolic dysfunction. B, Results for women. For a 70-year-old female patient, probability of death within 10 years increases from approximately 30% with normal diastolic function to mild dysfunction to 47% in those with moderate to severe diastolic dysfunction.

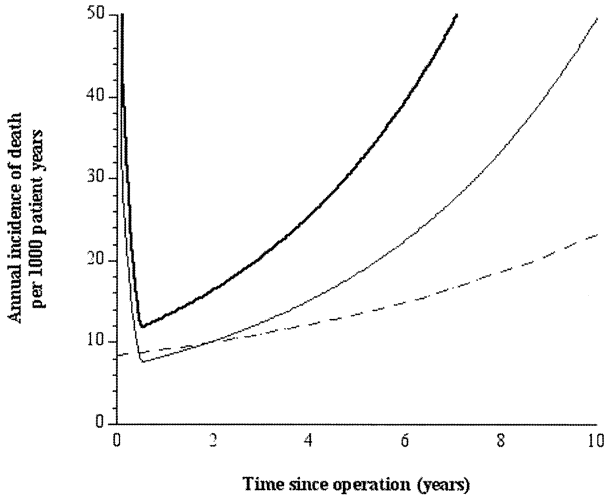

Figure 2. Risk of death associated with normal diastolic function to mild dysfunction or moderate to severe diastolic dysfunction compared with the general population. *Curves* show risk for a woman 65 years old at operation. *Bold line* indicates moderate to severe diastolic dysfunction; *narrow line* indicates normal diastolic function to mild dysfunction; *dashed line* indicates general population.

TABLE 2. The importance of preoperative diastolic dysfunction and time for mortality risk estimated by a Poisson model

	β	SE	P value
Constant	−6.95	1	<.0001
Current age	0.09	0.01	<.0001
Gender	−0.219	0.17	.23
Min(time, 1/12)*	−23.69	7.09	.0009
Max[min(time-1/12, 0.5-1/12), 0]†	−3.51	1.41	.01
Max(time-0.5, 0)‡	0.11	0.04	.005
Moderate to severe diastolic dysfunction	0.43	0.32	.19
Moderate to severe diastolic dysfunction times time	0.02	0.05	.67

*Reflecting change in risk per year during first month after surgery.
†Reflecting change in risk per year during second through sixth months after surgery.
‡Reflecting change in risk per year at more than 6 months after surgery.

sis and simultaneous coronary artery bypass grafting procedures did not differ.

Discussion

To our knowledge, this study represents the first large series of patients with severe aortic stenosis undergoing aortic valve replacement in which the importance of preoperative diastolic dysfunction has been investigated. As a major finding of potential clinical importance, we found that moderate to severe diastolic dysfunction estimated from Doppler echocardiography was an independent risk factor for late total mortality. The importance of preoperative moderate to severe diastolic dysfunction did not decrease with time. This finding suggests that moderate to severe diastolic dysfunction in patients with severe aortic stenosis is indicative of nonreversible structural myocardial changes that negatively affect survival.

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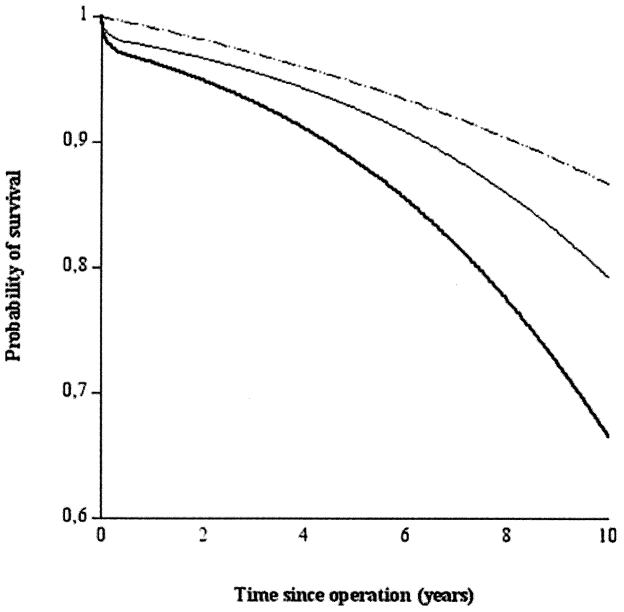

Figure 3. Importance of normal diastolic function to mild dysfunction or moderate to severe diastolic dysfunction for probability of survival. Curves were calculated from results of Poisson model in Table 2. *Bold line* indicates moderate to severe diastolic dysfunction; *narrow line* indicates normal diastolic function to mild dysfunction; *dashed line* indicates general population.

Left Ventricular Systolic Versus Diastolic Dysfunction

Interestingly, in this study, the LVEF did not independently predict the long-term outcome when diastolic function was considered. We can see two reasons for this. First, studies of systolic and diastolic function in patients with aortic stenosis show that diastolic dysfunction dominates[9,14] and probably precedes changes in myocardial contractility.[14] Hess and colleagues[15] demonstrated that 50% of patients with aortic stenosis had signs of diastolic dysfunction, despite normal systolic function. In this study, 24% of patients had an LVEF less than 50%, but 30% had moderate to severe diastolic dysfunction and another 12% had mild diastolic dysfunction with signs of impaired relaxation. Second, from previous studies of patients with pressure overload, we know that a reduced LVEF often reflects the afterload excess in patients with aortic stenosis, rather than true myocardial contractile dysfunction.[14,16]

We divided the patients, according to recommendations,[12] into four groups that reflected an increasing level of disease. The different flow velocity patterns in the mitral valve and pulmonary vein are primarily determined by the pressure gradient between the atrium and left ventricle. Patients with a normal left ventricular filling pattern or impaired relaxation are likely to have normal left ventricular compliance and normal left ventricular filling pressure. Patients with moderate to severe diastolic dysfunction are likely to have decreased left ventricular compliance and increased left ventricular filling pressure.[12] It could be argued that the importance of preoperative diastolic dysfunction should decrease with time in response to regression in myocardial hypertrophy and the normalization of myocardial structure.[17] In this study, we used a statistical method that enabled us to evaluate the impact with time. Importantly, we found that preoperative moderate to severe diastolic dysfunction indicated an unchanged or even increased postoperative mortality risk. This finding suggests that moderate to severe diastolic dysfunction in patients with aortic stenosis indirectly reflects nonreversible structural myocardial abnormalities that may eventually prove to be lethal.

Importance of Left Ventricular Hypertrophy and Prosthetic Type and Size

The negative impact of left ventricular hypertrophy on mortality among otherwise healthy individuals has been documented.[18] The aortic valve replacement procedure reduces left ventricular afterload, thereby starting a remodeling process that goes on for several years[19] and is prosthesis gradient dependent.[9] We hypothesized that among patients undergoing aortic valve replacement there would be individuals with important residual LV hypertrophy and that this might increase mortality. This was not the case, which raises questions about the importance of the prosthesis-patient mismatch issue.[20] In this study, patients with narrow aortic roots (size 19 or 21) received a mechanical prosthetic valve whenever possible to avoid the risk of prosthesis-patient mismatch with small stented biologic valves. This policy may have influenced the outcome, and we know from a study of a subgroup of these patients that those with prosthesis sizes 19 and 21 also had a reduction in LVM after 2 years.[9] Our patients consisted of an elderly, less active population. To recognize problems related to prosthesis-patient mismatch, the study group and the number of individuals with high activity levels should be larger, and the end point should include quality of life parameters. So, despite the important finding that the prosthesis size did not influence the long-term outcome in terms of mortality, we do not interpret our results as an argument against the prosthesis-patient mismatch problem.

In this study, we were not able to demonstrate any differences in outcome related to prosthesis type. We know from randomized trials comparing mechanical and biologic valves in the aortic position that problems with the biologic valve from valve deterioration start 10 to 12 years after the operation.[21,22] After 20 years of follow-up, Oxenham and associates[22] were not able to demonstrate any differences in mortality between groups with mechanical and biologic prosthetic valves. When reoperation or death was used as an end point, however, the mechanical prosthetic valve had a better outcome. Our results, in terms of survival after 12 years of follow-up, therefore agree with those of other

TABLE 3. Patients with normal diastolic function to mild dysfunction or moderate to severe diastolic dysfunction: clinical and echocardiographic characteristics

	Normal to mild (n = 210)	Moderate to severe (n = 89)	*P* value
Age (y)	68.6 ± 9.3	73.5 ± 7.4	<.0001
Sex (% male)	51	62	.08
Biologic prosthesis (%)	28	37	.15
Coronary artery bypass grafting (%)	38	47	.17
Mortality (%)	38	67	<.0001
Left ventricular mass index (g/m^2)	159 ± 43	171 ± 43	.08
LVEF (%)	61 ± 12	54 ± 16	<.0001
Stroke volume (mL)	75 ± 22	65 ± 23	.001
Cardiac output (L/min)	5.2 ± 1.7	4.2 ± 1.5	<.0001
Left atrial area (cm^2)	23 ± 5	27 ± 7	<.0001
Tricuspid valve gradient (mm Hg)	24 ± 7	34 ± 14	<.0001
Maximum gradient (mm Hg)	94 ± 29	94 ± 32	.9
Mean gradient (mm Hg)	58 ± 18	58 ± 20	.7
EOA/BSA (cm^2/m^2)	0.38 ± 0.11	0.33 ± 0.10	.002

Data are mean ± SD. *EOA/BSA,* Ratio of effective orifice area to body surface area.

investigators, but the findings should be interpreted with care.

Limitations

First, diastolic function was not evaluated with invasive catheter measurements, which is the criterion standard. We used different mitral and pulmonary vein filling patterns to grade the severity of diastolic dysfunction; although well documented, this is an indirect and categoric method.[12] Because of technical difficulties, we were not able to measure the isovolumetric relaxation time or the duration of the flow reversal during atrial systole in the pulmonary vein. Adding these parameters might have improved the grading of severity.[23] Second, we assumed that moderate to severe diastolic dysfunction represented intrinsic myocardial properties related to possible negative effects on outcome. To our knowledge, there are no reports on the correlation between the Doppler echocardiographic grading of diastolic function and myocardial composition or histopathologic changes in patients with aortic stenosis. even if these assumptions have not been proved or validated, however, the important message is that the left ventricular filling pattern studied with Doppler echocardiography contains important prognostic information.

References

1. Bonow RO, Carabello B, de Leon AC Jr, Edmunds LH Jr, Fedderly BJ, Freed MD, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation.* 1998;98:1949-84.
2. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med.* 2000;343:611-7.
3. Otto C. Aortic stenosis—listen to the patient, look at the valve. *N Engl J Med.* 2000;343:652-4.
4. Morris JJ, Schaff HV, Mullany CJ, Rastogi A, McGregor CG, Daly RC, et al. Determinants of survival and recovery of left ventricular function after aortic valve replacement. *Ann Thorac Surg.* 1993;56: 22-30.
5. Lund O, Flo C, Jensen FT, Emmertsen K, Nielsen TT, Rasmussen BS, et al. Left ventricular systolic and diastolic function in aortic stenosis. Prognostic value after valve replacement and underlying mechanisms. *Eur Heart J.* 1997;18:1977-87.
6. Connolly HM, Oh JK, Orszulak TA, Osborn SL, Roger VL, Hodge DO, et al. Aortic valve replacement for aortic stenosis with severe left ventricular dysfunction. Prognostic indicators. *Circulation.* 1997;95: 2395-400.
7. González-Juanatey JR, García-Acuña JM, Fernandez MV, Cendón AA, Fuentes VC, García-Bengoechea JB, et al. Influence of the size of aortic valve prostheses on hemodynamics and change in left ventricular mass: implication for surgical management of aortic stenosis. *J Thorac Cardiovasc Surg.* 1996;112:273-80.
8. Sim EK, Orszulak TA, Schaff HV, Shub C. Influence of prosthesis size on change in left ventricular mass following aortic valve replacement. *Eur J Cardiothorac Surg.* 1994;8:293-7.
9. Bech-Hanssen O, Caidahl K, Wall B, Myken P, Larsson S, Wallentin I. Influence of aortic valve replacement, prosthesis type, and size on functional outcome and ventricular mass in patients with aortic stenosis. *J Thorac Cardiovasc Surg.* 1999;118:57-65.
10. Bech-Hanssen O, Wallentin I, Houltz E, Beckman Suurkula M, Larsson S, Caidahl K. Gender differences in patients with severe aortic stenosis: impact on preoperative left ventricular geometry and function, as well as early postoperative morbidity and mortality. *Eur J Cardiothorac Surg.* 1999;15:24-30.
11. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol.* 1986;57:450-8.
12. Rakowski H, Appelton C, Chan CL, Dumesnil JG, Honos G, Jue J, et al. Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography. *J Am Soc Echocardiogr.* 1996;9:736-60.
13. Breslow NE, Day NE. In: Statistical methods in cancer research. Lyon, France: IARC Scientific Publications; 1987. p. 131-5.
14. Villari B, Hess OM, Kaufmann P, Krogmann ON, Grimm J, Krayenbuehl HP. Effect of aortic valve stenosis (pressure overload) and regurgitation (volume overload) on left ventricular systolic and diastolic function. *Am J Cardiol.* 1992;69:927-34.

15. Hess OM, Villari B, Krayenbuehl HP. Diastolic dysfunction in aortic stenosis. *Circulation.* 1993;87(5 Suppl):IV73-6.
16. Grossman W. Cardiac hypertrophy: Useful adaptation or pathologic process? *Am J Med.* 1980;69:576-84.
17. Villari B, Vassalli G, Betocchi S, Briguori C, Chiariello M, Hess OM. Normalization of left ventricular nonuniformity late after valve replacement for aortic stenosis. *Am J Cardiol.* 1996;78:66-71.
18. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med.* 1990;322:1561-6.
19. Monrad ES, Hess OM, Murakami T, Nonogi H, Corin WJ, Krayenbuehl HP. Time course of regression of left ventricular hypertrophy after aortic valve replacement. *Circulation.* 1988;77:1345-55.
20. Rahimtoola S. The problem of valve prosthesis-patient mismatch. *Circulation.* 1978;58:20-4.
21. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol.* 2000;36:1152-8.
22. Oxenham H, Bloomfield P, Wheatley DJ, Lee RJ, Cunningham J, Prescott RJ, et al. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprosthesis. *Heart.* 2003;89:715-21.
23. Rossvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. *J Am Coll Cardiol.* 1993;21:1687-96.